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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,773	06/21/2001	Guy W. Bemis	VPI94-04DIV5	6928

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[REDACTED] EXAMINER

LUKTON, DAVID

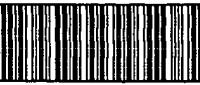
[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1653

DATE MAILED: 01/06/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. <b>09/886,773</b>	Applicant(s) <b>Bemis</b>	
	Examiner <b>David Lukton</b>	Art Unit <b>1653</b>	
<i>-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --</i>			
<b>Period for Reply</b> A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.			
- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication. - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely. - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). - Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).			
<b>Status</b>			
1) <input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>Oct 24, 2002</u>			
2a) <input type="checkbox"/> This action is FINAL.      2b) <input checked="" type="checkbox"/> This action is non-final.			
3) <input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11; 453 O.G. 213.			
<b>Disposition of Claims</b>			
4) <input checked="" type="checkbox"/> Claim(s) <u>76, 102-107, 118, and 125-128</u> is/are pending in the application.			
4a) Of the above, claim(s) <u>76, 105-107, 118, and 126-128</u> is/are withdrawn from consideration.			
5) <input checked="" type="checkbox"/> Claim(s) <u>102-104</u> is/are allowed.			
6) <input checked="" type="checkbox"/> Claim(s) <u>125</u> is/are rejected.			
7) <input type="checkbox"/> Claim(s) _____ is/are objected to.			
8) <input type="checkbox"/> Claims _____ are subject to restriction and/or election requirement.			
<b>Application Papers</b>			
9) <input type="checkbox"/> The specification is objected to by the Examiner.			
10) <input type="checkbox"/> The drawing(s) filed on _____ is/are a) <input type="checkbox"/> accepted or b) <input type="checkbox"/> objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).			
11) <input type="checkbox"/> The proposed drawing correction filed on _____ is: a) <input type="checkbox"/> approved b) <input type="checkbox"/> disapproved by the Examiner. If approved, corrected drawings are required in reply to this Office action.			
12) <input type="checkbox"/> The oath or declaration is objected to by the Examiner.			
<b>Priority under 35 U.S.C. §§ 119 and 120</b>			
13) <input type="checkbox"/> Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) <input type="checkbox"/> All b) <input type="checkbox"/> Some* c) <input type="checkbox"/> None of: 1. <input type="checkbox"/> Certified copies of the priority documents have been received. 2. <input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____. 3. <input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).			
*See the attached detailed Office action for a list of the certified copies not received.			
14) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e). a) <input type="checkbox"/> The translation of the foreign language provisional application has been received.			
15) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.			
<b>Attachment(s)</b>			
1) <input type="checkbox"/> Notice of References Cited (PTO-892)		4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____	
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)		5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)	
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____		6) <input type="checkbox"/> Other: _____	

Applicants' election of Group 1 is acknowledged (claims 102-104, and 125, drawn to compounds and compositions, with the proviso that G5 is excluded). Applicants have also attempted to comply with the "election of species" requirement by electing compound "O" in claim 103. However, it appears that the first compound listed (page 342, lines 14+) is compound "Q", rather than compound "O". The assumption at this point is that the elected specie is the first compound listed in claim 103.

Claims 76, 102-107, 118, 125-128 remain pending. Claims 102-104 are examined in this Office action; claim 125 is examined in part.

\*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 125 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown that some of the claimed compounds will inhibit interleukin-1- $\beta$  converting enzyme *in vitro*. Claim 125 is rejected because of the recitation of

"pharmaceutical". This term carries with it an implied assertion of therapeutic efficacy; it remains to be determined whether in fact any therapeutic benefit will accrue. Numerous hurdles remain to be overcome in making the transition from the test tube to the intact organism. Accordingly, the specification does not teach the skilled biochemist to use the claimed "pharmaceutical" compositions to sucessfully treat human disease.

It is noted preemptively that Ku (*Cytokine* 8, 377, 1996), discloses that there exist at least two compounds which inhibit "ICE", and which also show some benefit in a mouse model of type-II collagen-induced arthritis. However, this does not mean that other compounds which also inhibit ICE to some degree will also be therapeutically effective. A key issue is that of relative efficacies at ICE inhibition. If the inhibitor efficacy of applicants' claimed compounds falls short of the efficacy of the "Ku" compounds, there is no reason to expect efficacy in treatment of arthritis, or any other disorder. As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. One can look to applicants' own data in the specification for evidence of unpredictability in structure/activity relationships. [Additional data on structure/activity relationships can be found in the following: Dolle (*J.*

*Med. Chem.* **39**, 2438, 1996); Dolle (*J. Med. Chem.* **40**, 1941, 1997); Dolle (*J. Med. Chem.* **37**, 563, 1994); Dolle (*J. Med. Chem.* **38**, 220, 1995); Dolle (*J. Med. Chem.* **37**, 3863, 1994)]. As is evident, a minor structural change can lead to more than a 10-fold reduction in activity. Clearly, one cannot predict ICE inhibitory capability merely by looking at the structure of a compound. Moreover, the *in vitro* experiments were not done under identical conditions in the instant application as compared with the experiments done by Ku. Accordingly, attempting to extrapolate from the in vitro data disclosed in this application to the therapeutic results obtained by Ku leads to "unpredictable" results.

Consider also the following:

- Frost Robert A. (*American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **283** (3) R698-709, 2002) investigated the regulation of TNF $\alpha$  and IL-6 by lipopolysaccharide (LPS) in C2C12 myoblasts and mouse skeletal muscle. Treatment of myocytes with IL-1 or TNF-alpha also increased IL-6 mRNA content, and the increase in IL-6 mRNA due to LPS could not be prevented by pretreatment with antagonists to either IL -1 or TNF. Thus, even if applicants could successfully block all interleukin-1 production using the claimed compounds, interleukin-6 levels could not be controlled, thereby leading to "unpredictable" results on inflammatory response.
- Meyers K. P. (*Inflammation* **17** (2) 121-34, 1993) discloses that interleukin-1 receptor antagonist was not active as an antiinflammatory agent in the 24-h pleurisy model (carageenan-induced pleurisy).
- Rosenbaum J. T. (*Archives of Ophthalmology* **110** (4) 547-9, 1992) discloses that interleukin-1 receptor antagonist did not produce significant reduction in inflammation subsequent to an active Arthus reaction or subsequent to the intravitreal injection of 125 ng of endotoxin. Rosenbaum suggests that the failure of IL-1RA to be therapeutically effective may be due in part to the presence of other pro-

inflammatory cytokines.

- Brennan (*Clinical and Experimental Immunology* 81, 278-85, 1990) discloses that TGF- $\beta$  was effective to inhibit IL-1 $\beta$  production in LPs-stimulated peripheral blood mononuclear cells, but only if the cells were pretreated with TGF- $\beta$ . The IL-1 $\beta$  production was not inhibited if the TGF- $\beta$  was applied after the inducing stimulus. The point here is that if a scientist has evidence that a given agent "X" is effective to inhibit production of IL-1 $\beta$  when used prior to stimulation of cells (which stimulation produces the IL-1 $\beta$ ), attempting to inhibit production of IL-1 $\beta$  by using agent "X" after stimulation of the cells leads to "unpredictable" results.
- Paris (*Journal of Infectious Diseases* 171, 161-69, 1995) discloses that IL-1RA was not effective to treat inflammation caused by gram-negative bacteria.

Thus, attempting to extrapolate from *in vitro* ICE inhibition to treatment of human disease leads to "unpredictable" results. It is suggested that the term "pharmaceutical" be deleted from claim 125.

\*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claim 125 is rejected under 35 U.S.C. §103 as being unpatentable over Dolle (USP 5,985,838).

Dolle discloses various compounds such as those in col 22, line 42+. Also disclosed (e.g., col 8, line 39+) are pharmaceutical compositions. Dolle does not single out any of these compounds (col 22, line 42+) for combination with a carrier, but the ordinarily skilled artisan would recognize that these compounds are intended for this purpose.

Each of the Dolle compounds falls within the scope of claim 105. While claim 105 may not be directly at issue, claim 125 is at issue. The compounds of claim 105 are obtained when substituent variable R<sub>9</sub> (instant variable) is a one-carbon alkyl group (i.e., methylene) which is substituted once with oxo, and one with aryl.

Thus, the claim is rendered obvious.

\*

Claim 125 is rejected under 35 U.S.C. §103 as being unpatentable over Chapman (USP 5430128).

Chapman discloses various compounds falling within the scope of claim 105. Also disclosed is pharmaceutical compositions. One such compound falling within the scope

of claim 105 is the compound at col 16, line 42+; another example is the compound depicted at col 18, line 53+. It would have been obvious to the ordinarily skilled artisan to combine each of these compounds with pharmaceutically acceptable carriers.

\*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



DAVID LUKTON  
PATENT EXAMINER  
GROUP 1800